IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Jordan J.N. Tang and Arun K. Ghosh

Serial No.: 09/506,988 Art Unit: 1625

Filed: February 18, 2000 Examiner: D. Margaret M. Seaman

For: *PROTEASE INHIBITORS THAT OVERCOME DRUG RESISTANCE*

Assistant Commissioner for Patents
Washington, D.C. 20231

REPLY BRIEF

Sir:

This is a Brief in reply to the Examiner's Answer mailed September 24, 2003. A Request for Oral Hearing accompanies this Reply along with the appropriate fee of $145.00 for a small entity. It is believed the no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(3) STATUS OF CLAIMS ON APPEAL

The Examiner's answer mailed September 24, 2003 indicated that claims 5 and 11 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 1, 2, 4, 6-8, 10, and 12 are pending and rejected under 35 U.S.C. § 112, first paragraph enablement and written description and under 35 U.S.C. §102(b).

(6) ISSUES ON APPEAL

The issue presented on appeal is:

(1) whether claims 1, 2, 4, 6-8, 10 and 12 are enabled under 35 U.S.C. § 112, first paragraph.

(2) whether claims 1, 2, 4, 6-8, 10 and 12 comply with the written description under 35 U.S.C. § 112.

(3) whether claims 1, 2, 4, 6-8, 10, and 12 are disclosed under 35 U.S.C. § 102(b) by U.S. Patents Nos. 5,491,149 and 5,683,999 to Jadhav.

(8) Response to Examiner's Arguments

(a) The Claimed Invention

The application describes the synthesis of an aspartic protease inhibitor containing two isosteres (two hydrolysis sites), which binds more tightly to the active site of aspartic acid proteases then inhibitors containing a single isostere. One who is skilled in the art would be aware of the numerous examples of aspartic acid inhibitors containing a single isostere. No art discloses two isosteres in the same compound, however. However, the observation that incorporation of a second isostere does not destroy the activity could not be predicted. Accordingly, the prior art neither discloses nor makes obvious a compound containing two isosteres.

The Examiner is confused regarding the definitions of isostere and transition state isostere. One of ordinary skill in the art defines isosteres as molecules or ions of similar size containing the same number of atoms and valence electrons. Transition state isosteres are groups of atoms of similar size, containing the same number of atoms and valence electrons, which

mimic the reaction site in the transition state of a catalyzed reaction. The claims in this application are drawn to a polypeptidic inhibitor containing two isosteres, each of which is able to mimic the scissible (peptide) bond in the transition state of the catalytic mechanism of aspartic proteases.

(b) Rejections Under 35 U.S.C. § 112, enablement

The legal standard for enablement is that the teachings of the specification would allow one skilled in the art to make and/or use the invention. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement are: 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The breadth of the claims: Aspartic acid proteases hydrolyze peptide linkages resulting in the formation of a free amine and free carboxylate group. The transition state of the mechanism involves the partial breaking of the peptide bond leading to the formation of a tetrahedral nitrogen. The amine is the leaving group in this reaction. The incorporation of an isostere introduces a pair of covalently linked atoms (one of which is usually C), which are already in tetrahedral conformations and thus cannot act as leaving groups. Due to the chiral nature of the active site, stereochemical control of the isostere is necessary as well. The prior art describes

numerous examples and provides enabling descriptions of various single stereoisomers. Furthermore, extensive studies of the active site of aspartic proteases have provided additional structural information regarding amino acid side chains that must be present in the inhibitor in order for it to bind to the active site. The introduction of the isostere itself without the supporting peptide structure would be ineffective as an inhibitor (Examiner's reference to 1,3-butyleneglycol).

The nature of the invention: The nature of the invention is aspartic acid protease inhibitors which incorporate two transition-state isosteres. These exhibit a higher binding affinity for the active site, exhibit significantly better activity against HIVPr-resistant mutants and are less prone to development of resistance.

The state of the prior art: The prior art describe several compounds that have a single transition-state isostere which mimics a substrate peptide with a single hydrolysis site. Because each residue in the inhibitor binds only one subsite of the enzyme, HIV-I is able to develop resistance/mutation to the inhibitor. There are no examples in the prior art of compounds containing two isosteres which exhibit the observed activity as demonstrated by appellants.

The level of predictability in the art: The specification discloses an aspartic protease inhibitor incorporating two isosteres, with increased binding affinity and significantly improved activity against HIVPr-resistant mutants. The Appellants have provided many examples of inhibitory isosteres, all sharing a common feature: structures predicated on the target structure/sequence to which they bind. Compounds such as hydroxyethylene, dihydroxyethylene, hydroxyethylamine, phosphinate, reduced amide, and other examples are

well illustrated in Vacca *et al.* (See page 12, lines 22-25, in Vacca *et al.*, *Design of Tight Binding Human Immunodeficiency Virus Type 1 Protease Inhibitors*, *Methods in Enzymology*, 241, 313-333, 1994; submitted with Information Disclosure Statement mailed on July 25, 2000). The specification describes two compounds incorporating two isosteres. UIC-98-056 contains two isosteres, both of which are hydroxyethylene and a second compound, where the two hydroxyethylene isosteres are substituted with two other kinds of isosteres. Based on the teachings of the specification, one who is skilled in the art would predict that a compound incorporating any two of the isosteres disclosed in the specification would observe the enhanced activity demonstrated by the Appellants for these representative compounds.

The amount of direction provided by the inventor: The Examiner appears to define a transition-state isostere in the present specification as a discrete molecule. A transition-state isostere consists of a group of atoms incorporated into a larger molecule composed of amino acid residues. In the present specification, the transition-state isosteres consist of two tetrahedral atoms (C or N) covalently linked and incorporated into a larger molecule composed of amino acid residues. The transition state isosteres mimic the peptide bond that is hydrolyzed by the aspartic acid proteases. The tetrahedral geometry of the isosteres is in contrast to the planar nature of the scissible peptide bond and the lack of a suitable leaving group imparts the inhibitory activity. Furthermore, the presence of two transition-state isosteres, both of which mimic the scissible peptide bond, makes it more difficult for aspartic acid proteases to develop resistant mutants to this class of inhibitors (pg. 9, lines 14-32; pg. 10, lines 1-31).

The synthesis of aspartic acid protease inhibitors containing one transition-state isostere is well known in the prior art. See Figure 1 and Table II at page 18, for example. The specification does disclose the synthesis of two inhibitors containing two transition-state isosteres. One with ordinary skill in the art of organic synthesis could make and use inhibitors of aspartic acid proteases containing two transition-state isosteres using the teachings of the specification. See page 10.

The existence of working examples. There is no legal requirement that all of the examples in the patent specification actually be reduced to practice before the filing of the application; it is only required that the specification contain a disclosure which enables those skilled in the art to practice the invention. *Corning Glass Works v. Sumitomo Electric USA Inc.*, 5 USPQ2d 1545, 1562 (S.D. N.Y. 1987) , *aff'd*, 868 F.2d 1251, 9 USPQ2d 1962 (Fed. Cir. 1989). As the examiner has acknowled, appellants have synthesized, and tested the activity of, an inhibitor containing two transition-state isosteres. Appellants have also provided additional data on how other two transition-state isosteres could be made. The prior art also teaches a number of different isosteres that can be made. In combination, those skilled in the art would have no trouble making and using the claimed two isostere compounds.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The Examiners claims that the quantity of experimentation needed to make the instant invention is undue due to the lack of direction provided by the Appellantss. We respectfully disagree. The synthesis of aspartic acid proteases inhibitors containing a single transition-state isostere is well understood in the art. The requirement that certain side chains

must be present in the inhibitor in order for effective binding in the active site has also been described. The present specification teaches that the incorporation of a second transition-state isostere moiety into the inhibitor results in enhanced activity. The teachings of the instant specification in conjunction with knowledge of the art would clearly enable the ordinary artisan to make or use the class of compounds described in the specification.

(c) Rejection under 35 U.S.C. §112, written description

The first paragraph of 35 U.S.C. § 112 sets forth the written description requirement for patents as follows:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The standard regarding what is or is not supported by the specification has been clearly articulated as "requiring the specification to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, the inventor was in possession of the invention", i.e., whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111, 1117 (Fed . Cir. 1991). Compliance with the written description requirement is essentially a fact-based inquiry that will "necessarily vary depending on the nature of the invention claimed." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (citing *In re DiLeone*, 436 F.2d 1404, 1405 (CCPA 1971)).

Compliance with the first paragraph of § 112 is adjudged from the perspective of person skilled in the relevant art. *Application of Smith*, 481 F.2d 910, 914 (CCPA 1973). The claimed subject matter need not be described in *haec verba* in the specification in order for that specification to satisfy the description requirement, *In re Smith*, 458 F.2d 1389 (CCPA 1972); *In re Lukach*, 442 F.2d 967 (CCPA 1971). "[T]he test for sufficiency of support in a parent application is whether the disclosure of the application...reasonably conveys to the artisan that the inventor had possession at that time of the...claimed subject matter." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)(internal quotes and citations omitted). When the original specification accomplishes that, regardless of how it accomplishes it, the essential goal of the description requirement is realized. See, e. g., *In re Smythe*, 480 F.2d 1376 (CCPA 1973).

The fact that the specification describes the invention prophetically does not violate the written description requirement. In *Snitzer v. Etzel*, 465 F.2d 899, 175 USPQ 108 (CCPA 1972) (an interference case), the court stated:

> [W]e fail to see the relevance of the listing of several inoperative species when the species claimed is operative and performs as "speculated." Whether it is labeled "discovery" or "speculation," appellant's conception of [the claimed composition] is no less his own, no less original, no less important technologically, and, on this record, earlier than appellees'. His constructive reduction to practice by filing a patent application disclosing the conception and setting in motion the steps by which the public will be apprised of the discovery is

in no way diminished if the conception is characterized as "speculation" or if other related conceptions turn out to be practically or technically unsound.

Id. at 902-03, 175 USPQ at 111.

The inquiry into whether or not there is an adequate written description is not performed in a vacuum. "Knowledge of one skilled in the art is relevant to meeting [the written description] requirement." *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. Apr. 2, 2002) (slip op.), vacating a prior decision, *Enzo Biochem, Inc. v. Gen-Probe*, 285 F.3d 1013, 62 USPQ 2d 1289 (Fed. Cir. April 2, 2002), and reversing the district court's grant of summary judgment that Enzo's claims are invalid for failure to meet the written description requirement, stating in relevant part:

"The PTO has issued Guidelines governing its internal practice for addressing that issue. The Guidelines, like the Manual of Patent Examining Procedure ("MPEP"), are not binding on this court, but may be given judicial notice to the extent they do not conflict with the statute. See Molins PLC v. Textron, Inc., 48 F.3d 1172, 1180 n.10, 33 USPQ2d 1823, 1828 n.10 (Fed. Cir. 1995). In its Guidelines, the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106 (emphasis added). The PTO Guidelines clearly state that the written description requirement can be met by "showing that an invention is complete by disclosure of

sufficiently detailed, relevant identifying characteristics....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Guidelines, 66 Fed. at 1106." (emphasis added) *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. July 15, 2002).

The general principle of the written description requirement for a claimed genus may be satisfied through (1) sufficient description of a representative number of species by actual reduction to practice, (2) reduction to drawings of a general structure, or (3) disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, (4) describing functional characteristics coupled with a known or disclosed correlation between function and structure, or (5) a combination of such identifying characteristics, sufficient to show the appellant was in possession of the claimed genus. Reagents of the University of California v. Eli Lilly, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Using the correct legal analysis, appellants have clearly provided a written description of the claimed genus of compounds having a peptide backbone and including two isosteres.

(d) Rejections Under 35 U.S.C. § 102(b)

Claims 1,2, 4, 6-8, 10 and 12 were rejected under 35 U.S.C. 102(b) as anticipated by U.S. Patent No. 5,491,149, "Jadhav 1" or U.S. Patent No. 5,683,999, "Jadhav2". Jadhav 1 discloses compounds that are aspartic acid protease inhibitors. These compounds contain a single isostere, ***not*** two isosteres as claimed. An inhibitor of aspartic acid proteases must incorporate an isostere which mimics the peptide bond that is hydrolyzed by the protease. The peptide bond

consists of two atoms: a tetrahedral nitrogen and a trigonal planar carbon. The isostere must include two atoms, preferably in a tetrahedral geometry, in order to mimic the peptide bond. The compounds in Jadhav 1 contain a single dihydroxyethylene moiety and thus only a single isostere. Jadhav 2 discloses a class of inhibitors incorporating a cyclic urea. These compounds also contain a single dihydroxyethylene moiety and thus only a single isostere. The claims define compounds with *two* hydroxyethylene moieties incorporated into the structure of the inhibitor and thus having two transition-state isosteres. The compounds disclosed by Jadhav 1 and 2 mimic only one scissible peptide bond and thus would be subject to the same mechanism of resistance/mutant formation as previously reported. The claimed compounds contain two transition state isosteres which mimic two different scissible peptide bonds. This class of compounds exhibits a stronger binding affinity for the active site of aspartic acid proteases than single transition-state isosteres, exhibit significantly increased activity against HIVPr-resistant mutants and are less prone to the development of resistance.

(9) SUMMARY AND CONCLUSION

Aspartic acid protease inhibitors containing a single transition-state isostere and the ability of these inhibitors to mimic a peptide bond with a single hydrolysis site have been described in the prior art. These compounds have been shown to be clinically effective providing further evidence that isostere inhibition is well know in the art. Therefore, one of skill in the art would be familiar with the synthesis and characterization of these compounds.

The present specification describes two inhibitors of aspartic acid proteases containing two transition-state isosteres. These inhibitors exhibit increased binding affinity for the active

site of the protease, as well as significantly better activity against HIVPr-resistant mutants. The induced-fit model of enzyme-substrate binding reveals that enzymes have a high specificity for a single substrate and that chemical modifications of that substrate can dramatically affect binding affinity. The specification clearly describes the synthesis of an inhibitor containing two transition-state isosteres (UIC-98-056). The synthesis of other inhibitors incorporating two transition-state isosteres would not require undue experimentation based upon the teachings of the specification in combination with the prior art.

Jadhav 1 and 2 discloses aspartic acid protease inhibitors incorporating a single dihydroxyethylene moiety. The dihydroxyethylene group mimics a single peptide bond (hydrolysis site). As a result, it is susceptible to the same mechanism of mutant-resistance formation as previously described single transition-state isostere inhibitors.

Accordingly, the claimed compounds are novel, enabled, and comply with the written description requirement.

U.S.S.N. 09/506,988
Filed: February 18, 2000
REPLY BRIEF

Allowance of claim 1, 2, 4-8, and 10-12 is respectfully solicited.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 31,284

Date: November 24, 2003
HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8473
(404) 817-8588 (fax)

1384065_v1

OMRF 176
078617/00014